below and then the counter-arguments made in the Final Office Action are addressed.

Bannerjee is not necessarily prior art to the instant application. The Bannerjee publication is of an application filed May 3, 2002, which is a divisional of an application filed June 22, 2001. The filing dates of both of these applications are after applicants' filing date of May 16, 2001. The publication also indicates priority to a provisional application filed April 17, 2001. The Bannerjee publication is only prior art to applicants' filing date for what has an enabling disclosure in the provisional application. The record does not indicate what the provisional application discloses. Following the refusal of the Examiner in the last Office Action to provide applicants with a copy of provisional disclosure, applicants have made multiple attempts over the last two months to obtain a copy of the disclosure from the PTO. The PTO at first provided the wrong document and, since then, has refused to provide the correct document for copying, despite numerous requests. Also, it is not available electronically on the PTO's Public PAIR system. Considering these circumstances, applicants again request that the Examiner provide applicants with a copy of the provisional application disclosure. In this context, it is again pointed out that the Examiner has the burden of providing documentary support for the rejection and, without the provisional disclosure, support for the rejection is currently lacking.

Even if it is assumed, for argument purposes, that the Bannerjee provisional supports all the disclosure of the publication, there is still not proper motivation to combine the references as suggested in the rejection and, even if combined, the combination would not suggest the claimed invention. Miller teaches compositions and methods for stabilizing radiolabeled peptides and proteins. Miller lacks any teaching or suggestion of including in its compositions a compound which provides or generates iodide ions. Bannerjee teaches compositions and methods for treating symptoms of bronchoconstrictive disorders, such as

asthma. Bannerjee teaches the optional addition of tonicity adjusting agents to its compositions, paragraph [0056]. Among the 70 particular examples of various types of tonicity adjusting agents in Bannerjee are potassium iodide and sodium iodide. There is no suggestion from the teachings of these references that a tonicity adjusting agent would be desired in the Miller compositions. Miller makes no suggestion at all regarding tonicity adjusting agents or that tonicity is a concern and Bannerjee suggests only that tonicity adjusting agents might be useful in its bronchodilating compositions. The Miller and Bannerjee compositions are completely different in the nature of the components therein and in their function and use. Even if one of ordinary skill in the art were motivated to add a tonicity adjusting agent to the Miller compositions, there is nothing to suggest that the tonicity adjusting agents of Bannerjee would be a suitable choice. One of ordinary skill in the art would have no reasonable expectation from the reference teachings that a tonicity adjusting agent of Bannerjee for bronchodilating compositions would be effective in a radiolabeled peptide or protein composition of Miller.

Even if the unmotivated combination of adding a tonicity adjusting agent of Bannerjee to the Miller compositions were made, the claimed invention would still not be suggested. There are no teachings in the art which would direct one of ordinary skill in the art to pick potassium iodide or sodium iodide from among the 70 types of tonicity adjusting agents of Bannerjee. Absent some direction or blazemarks in the reference teachings to make such a particular selection, motivation is lacking and this particular combination is not obvious.

As an additional independent basis for nonobviousness, the references fail to teach or suggest use of an iodide agent such that it "stabilizes the composition against degradation thus maintaining high radiochemical purity of the composition." Certainly, there is no

suggestion from the references of a "method for stabilizing a composition .. to lessen the occurrence of the radionuclide degrading." See, e.g., claim 11 and claims dependent thereon. The references provide no suggestion at all regarding such function. Tonicity agents are used to adjust pharmaceutical compositions to the individual needs of a patient. Such adjustments are made right before the administration of the pharmaceutical to the individual patient. Otherwise, the tonicity cannot be adjusted to the actual individual needs of patient. The fresh tonicity-adjusted pharmaceutical composition is not meant to be stored for a longer period of time. The usual clinical routine is that after individually adjusting tonicity, the pharmaceutical is administered as fast as possible in order to avoid any oxidation or other detrimental effects. Accordingly, one of ordinary skill in the art would have had no expectation that tonicity adjusting agents would have any effect on prolonging stability and thereby shelf-life of the composition. To the contrary, one of ordinary skill in the art would not consider that an agent used for adjusting tonicity immediately before administration of a composition would have any effect on stabilizing a composition. The current invention claims iodine salts having a surprising stabilizing effect in claimed pharmaceutical compositions in order to prolong shelf-life. Tonicity is not an issue in the current invention and comes into play only right before actual administration of a pharmaceutical, not during shelf-life which is prior to individual tonicity adjustment and intended actual administration. Miller in combination with Bannerjee does not render obvious the surprising effect of iodine salts stabilizing radiopharmaceutical compositions as claimed in the current invention and certainly does not suggest a **method** for stabilizing a composition to lessen the occurrence of the radionuclide degrading.

Blum, also directed to radiolabeled peptides, teaches nothing about combining iodide ions with a radiopharmaceutical. Thus, its combination fails to cure the above-noted

deficiencies of the prior art.

At page 5 of the Final Office Action, first full paragraph, it was argued that the motivation to combine need not be in the subject of the invention and that Bannerjee teaches the conventionality of adding tonicity agents to pharmaceutical formulations. In response, applicants urge that, while the art need not motivate a combination to meet the objects of the invention, there must be some type of motivation to make the combination and there is none here. Further, applicants respectfully disagree that Bannerjee teaches the conventionality of adding tonicity agents to pharmaceutical formulations. Bannerjee only teaches the optional consideration of adding tonicity adjusting agents to the particular type of brochodilating compositions disclosed in Bannerjee. Applicants urge that the PTO provide a citation to where Bannerjee teaches adding their listed tonicity agents to <u>any</u> pharmaceutical composition. At paragraph [0056], the references teaches optional use of those agents only in certain embodiments of the invention described therein. Further, the reason for the combination is certainly pertinent to the method claims. The references fail to provide any suggestion of combining the reference teachings to provide a method for "stabilizing a composition .. to lessen the occurrence of the radionuclide degrading."

At page 5 of the Final Office Action, second paragraph, it was argued that every composition has tonicity. This, of course, is true. But it is not true that every composition needs to have its tonicity adjusted. One of ordinary skill in the art is not motivated to add a tonicity adjusting agent to every composition. Certainly, one of ordinary skill in the art is not motivated to add an agent taught only to adjust tonicity of certain bronchodilating compositions to any other pharmaceutical composition, particularly to a completely unrelated radiolabeled peptide composition. There is no reasonable expectation of success in adding a tonicity adjusting agent of Bannerjee into the Miller compositions when there is no

suggestion that the Miller compositions need a tonicity adjustment and there is no suggestion that the agents of Bannerjee are useful in connection with radiolabeled peptide compositions or would be compatible – and not detrimental – to the function of the Miller compositions.

At page 5 of the Final Office Action, third paragraph, in conjunction with the points addressed above, it was argued that adjusting tonicity is beneficial. This is clearly not correct. If the tonicity of a composition is already in a suitable state without adding any tonicity adjusting agent, the addition of an agent to adjust tonicity can be detrimental, i.e., it can modify the tonicity to a state outside that desired. Further, any tonicity agent could have additional unwanted effects in a composition. There is no suggestion in the art that the tonicity adjusting agents listed by Bannerjee are compatible with radiolabeled peptide compositions. Finally, there is no suggestion that an agent which is effective to adjust tonicity of one type of composition will provide a similar effect in a completely different composition having a different utility.

At page 6 of the Final Office Action, first full paragraph, it was argued that the fact that each of Miller, Bannerjee and Blum are directed to pharmaceutical compositions for in vivo administration makes them all analogous art and, thus, apparently, any combination of the disclosures in these references can be made. In response, applicants urge that the principal of analogous art cannot be applied so broadly. Under such broad application, it would always be obvious to combine any components from any reference related to pharmaceuticals for in vivo administration. This clearly cannot be the proper law. As stated in Intra Corp. v. Hamar Laser, 4 USPQ2d 1337, 1352 (E.D.Mich. 1987), *aff'd*, 862 F.2d 320 (Fed. Cir. 1988) (unpublished): "Most patentable inventions combine old elements .. [and such] fact .. is irrelevant to the legal determination of obviousness under § 103..". See also In re Rouffet, 149 F.3d 1350, 47 USPQ 2d 1453 (Fed. Cir. 1998).

At page 6 of the Final Office Action, third paragraph, it was argued that Bannerjee was relied on for its teaching of tonicity adjusting agents and was considered as a whole. Applicants submit that, if it was relied on merely as teaching tonicity adjusting agents for any application, it was not considered as a whole. Bannerjee teaches only that the tonicity adjusting agents listed therein are optionally useful in connection with the bronchodilating compositions disclosed therein. This aspect of Bannerjee appears to have been ignored in alleging that Bannerjee teaches using the listed tonicity adjusting agents for any in vivo pharmaceutical composition.

At page 7 of the Final Office Action, first full paragraph, it was argued that the test for obviousness is simply what the combination of references makes obvious to one of ordinary skill in the pertinent art. Applicants respectfully disagree. The test first requires that there be sufficient motivation to make the combination of reference teachings in the first place. There is not sufficient motivation here, for the reasons already given. Further, when it is proper to combine the teachings of the references, the references' teachings must be considered as a whole. Thus, it must be considered that Bannerjee only teaches tonicity agents for bronchodilating agents which are completely unrelated to the Miller radiopharmaceutical compositions.

At page 7 of the Final Office Action, second full paragraph, it was argued that the combined references teach the instant composition and the properties inherently flow therefrom. In response applicants urge that it is never correct to say that a combination of references "teach" the composition. The term "teach" implies that the composition is exactly set forth, i.e., anticipated, which is clearly not the case. Inherency only comes up when a composition is specifically taught, not in an obviousness setting. An argument for obviousness based on inherency of a modification of the reference is only permissible if the

element alleged to be inherent is suggested from the prior art. There is no suggestion of the stabilizing properties of iodides in the prior art. Thus, this application of inherency is an impermissible use of hindsight; see, e.g., In re Rijckaert, 28 USPQ2d 1955 (Fed. Cir. 1993).

At page 7, of the Final Office Action, third paragraph, to page 8, it was argued that the claims do not recite an "amount sufficient." But the claims do recite "where the iodide ions aid in stabilizing the composition against degradation thus maintaining high radiochemical purity of the composition." It is inherent in those claims that, in order to have such effect, the iodide ions must be provided in amount sufficient to have such effect. That they do not contain these exact words is not the issue. The issue is whether the claims require a defined amount of the iodide ions. The functional language certainly requires an amount defined as sufficient to perform that function.

At page 8, first full paragraph, of the Final Office Action, a discussion was provided regarding hypotonic and hypertonic solutions. Applicants do not disagree with the statements, but, as addressed above, do not see how the discussion supports the rejection. There are still no teachings in the cited art that the Miller compositions are or would be expected to be either hypotonic or hypertonic. Also, there are no teachings in the cited art that, if they were, the Bannerjee agents would be useful for remedying such property. Finally, there are no teachings which would point one of ordinary skill in the art to pick, particularly, the two iodide agents out of the 70 listed by Bannerjee for use in Miller. The only suggestion for combining the references in a manner to support the rejection comes from using applicants own claims as a blueprint for picking out unconnected disclosures of the references to meet applicants' claims.

Furthermore, even if a prima facie case of obviousness was established by the references (which, for the reasons given, it is not), the unexpected properties of the claimed

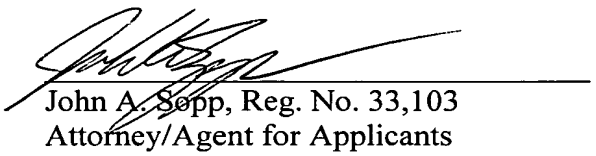
invention overcome any prima facie case of obviousness. One of ordinary skill in the art could not have expected from the reference teachings that the two iodide agents out of the 70 tonicity agents listed by Bannerjee could stabilize a radiopharmaceutical composition against degradation, thus, maintaining high radiochemical purity of the composition. The references provide no suggestion, whatsoever, of such advantageous activity. The unexpected advantageous properties of the selection of the iodide agents from among the many types disclosed by Bannerjee provides further convincing proof of the nonobviousness of the instant claims.

For all of the above reasons, it is again urged that the rejections under 35 U.S.C. § 103 should be withdrawn.

It is submitted that the application is in condition for allowance. But the Examiner is kindly invited to contact the undersigned to discuss any unresolved matters.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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